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ORIGINAL ARTICLE

Variation in *PCSK9* and *HMGCR* and Risk of Cardiovascular Disease and Diabetes

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ABSTRACT

BACKGROUND

Pharmacologic inhibitors of proprotein convertase subtilisin–kexin type 9 (PCSK9) are being evaluated in clinical trials for the treatment of cardiovascular disease. The effect of lowering low-density lipoprotein (LDL) cholesterol levels by inhibiting PCSK9 on the risk of cardiovascular events or diabetes is unknown.

METHODS

We used genetic scores consisting of independently inherited variants in the genes encoding PCSK9 and 3-hydroxy-3-methylglutaryl–coenzyme A reductase (HMGCR; the target of statins) as instruments to randomly assign 112,772 participants from 14 studies, with 14,120 cardiovascular events and 10,635 cases of diabetes, to groups according to the number of LDL cholesterol–lowering alleles that they had inherited. We compared the effects of lower LDL cholesterol levels that were mediated by variants in *PCSK9*, *HMGCR*, or both on the risk of cardiovascular events and the risk of diabetes.

RESULTS

Variants in *PCSK9* and *HMGCR* were associated with nearly identical protective effects on the risk of cardiovascular events per decrease of 10 mg per deciliter (0.26 mmol per liter) in the LDL cholesterol level: odds ratio for cardiovascular events, 0.81 (95% confidence interval [CI], 0.74 to 0.89) for *PCSK9* and 0.81 (95% CI, 0.72 to 0.90) for *HMGCR*. Variants in these two genes were also associated with very similar effects on the risk of diabetes: odds ratio for each 10 mg per deciliter decrease in LDL cholesterol, 1.11 (95% CI, 1.04 to 1.19) for *PCSK9* and 1.13 (95% CI, 1.06 to 1.20) for *HMGCR*. The increased risk of diabetes was limited to persons with impaired fasting glucose levels for both scores and was lower in magnitude than the protective effect against cardiovascular events. When present together, *PCSK9* and *HMGCR* variants had additive effects on the risk of both cardiovascular events and diabetes.

CONCLUSIONS

In this study, variants in *PCSK9* had approximately the same effect as variants in *HMGCR* on the risk of cardiovascular events and diabetes per unit decrease in the LDL cholesterol level. The effects of these variants were independent and additive. (Funded by the Medical Research Council and the National Heart, Lung, and Blood Institute.)

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Monoclonal antibodies and other therapies that inhibit proprotein convertase subtilisin–kexin type 9 (PCSK9) have been shown to reduce low-density lipoprotein (LDL) cholesterol levels by approximately 50 to 60% in several randomized trials.[1-8] Whether lowering LDL cholesterol levels by inhibiting PCSK9 will reduce the risk of cardiovascular events and, like statins, also increase the risk of new-onset diabetes is unknown.[9]

Exploratory and post hoc analyses of randomized trials have suggested that lowering LDL cholesterol levels by approximately 70 mg per deciliter (1.81 mmol per liter) with a PCSK9 inhibitor may reduce the risk of major cardiovascular events by up to 50%.[10,11] However, these trials included a total of fewer than 120 cardiovascular events, and data on the risk of new-onset diabetes are very limited. Four much larger and longer-term cardiovascular outcome trials are currently ongoing and will provide a much more robust estimate of the clinical effect of PCSK9 inhibitors.[12-15]

In anticipation of the results of those trials, we have used a "mendelian randomization" approach to test the effect of LDL cholesterol–lowering variants in *PCSK9* on the risk of cardiovascular events and diabetes. The results of a mendelian randomization study can be interpreted as follows: if a genetic variant (e.g., in *PCSK9*) is associated with an exposure of interest (e.g., LDL cholesterol levels) that is observationally associated with the outcome under study (e.g., coronary heart disease), then the observed association between the exposure and the outcome is likely to be causal if the variant is also associated with the outcome. If not, the observed association between the exposure and the outcome is likely to be noncausal. (For more information, see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Because PCSK9 inhibitors are designed to recapitulate the phenotype of loss-of-function mutations,[16,17] we used the presence of LDL cholesterol–lowering variants in *PCSK9* to estimate the biologic effect of inhibiting PCSK9 on both the risk of cardiovascular events and the risk of diabetes. We constructed genetic scores that mimic the effect of PCSK9 inhibitors and the effect of statins (which target 3-hydroxy-3-methylglutaryl–coenzyme A reductase [HMGCR]) and compared the effect of these scores on the risk of cardiovascular disease and the risk of diabetes to make inferences about the potential clinical benefit and safety of treatment with a PCSK9 inhibitor as compared with treatment with a statin.

Methods

Study Population

The study included 112,772 participants (with 14,120 cardiovascular events and 10,635 cases of diabetes) from 14 prospective cohort or case–control studies who had provided written informed consent for genetic studies and for whom individual participant-level data were available as part of the Database of Genotypes and Phenotypes program of the National Center for Biotechnology Information.[18] A description of the included studies and the genotyping platforms that were used in each study is provided in Table S1 in the Supplementary Appendix.

Genetic Instruments

We constructed genetic scores for *PCSK9* and *HMGCR* by combining all variants within 100 kb on either side of each gene that were associated with LDL cholesterol levels at a genomewide level of significance ($P<5.0\times10^{-8}$) as reported by the Global Lipids Genetics Consortium and that were in low linkage disequilibrium ($r^2<0.2$) with all other variants included in the score.[19,20] For each variant, we defined the exposure allele as the allele associated with lower LDL cholesterol levels.[19] For each study participant, we calculated a weighted *PCSK9* genetic score and a weighted *HMGCR* score by adding the number of LDL cholesterol–lowering alleles that the person had inherited at each variant that was included in either score, weighted by the effect of each variant on LDL cholesterol levels measured in milligrams per deciliter.[19]

Study Design

We dichotomized each genetic score and used this instrument to divide participants into two groups of approximately equal size on the basis of whether their genetic score was above the median or below the median (Fig. S1 in the Supplementary Appendix). Because each variant that was included in either genetic score is inherited approximately randomly at the time of con-

ception[21] and is inherited approximately independently of other variants included in the score owing to low linkage disequilibrium, the number of LDL cholesterol–lowering alleles that a person inherits in either score should also be random. Therefore, assignment to each group with the use of this instrument should be random. To evaluate the dose–response relationship, we divided participants into four groups on the basis of the quartile value of their genetic score. To compare the separate and combined effect of variants in *PCSK9* and *HMGCR*, we conducted a 2×2 factorial analysis (Fig. S1 in the Supplementary Appendix).

STUDY OUTCOMES

The primary cardiovascular outcome for the study was a composite of the first occurrence of myocardial infarction or death from coronary heart disease. Key secondary cardiovascular outcomes were major coronary events (defined as the first occurrence of myocardial infarction, coronary revascularization, or death from coronary heart disease) and major vascular events (defined as the first occurrence of a major coronary event or stroke). The primary safety outcome was diabetes, defined as either a glycated hemoglobin level greater than 6.5% or treatment with a glucose-lowering medication. Key secondary safety outcomes were fasting plasma glucose level, weight, and body-mass index. To increase the statistical power of the analyses, we combined prevalent and incident outcome events under the assumption that all events occur incident to a genetic exposure.

STATISTICAL ANALYSIS

We assessed whether the assignment to each group was indeed random by comparing the baseline characteristics of the participants in each group. We measured the difference in LDL cholesterol level between groups using linear regression and compared the risk of cardiovascular events or diabetes using logistic-regression analyses that were adjusted for age and sex. To compare the effect of different variants or genetic scores on the risk of cardiovascular events and diabetes, we adjusted each effect size estimate for a standard decrement of 10 mg per deciliter (0.26 mmol per liter) in the LDL cholesterol level using the usual ratio of effect estimates method (for details, see the Methods section in the Supplementary Appendix).

All analyses were performed separately in each of the included studies and then combined across studies in a fixed-effects inverse-variance–weighted meta-analysis to produce summary estimates of effect. To minimize the potential for bias with respect to population stratification, separate analyses were performed for each included ancestral group before being combined.

In a test of replication, we compared the effect of lower LDL cholesterol levels on the risk of coronary heart disease mediated by the *PCSK9* and *HMGCR* genetic scores in up to 62,240 case patients and 127,299 controls without such disease who were enrolled in the Coronary Artery Disease Genomewide Replication and Meta-Analysis plus the Coronary Artery Disease (CARDIoGRAMplusC4D) consortium studies and in up to 86,196 participants of European descent (with 22,669 cases of diabetes) who were enrolled in the Diabetes Genetics Replication and Meta-Analysis (DIAGRAM) consortium studies (Table S2 in the Supplementary Appendix).[22-24] Pleiotropy was assessed with the use of mendelian randomization–Egger regression.[25] All analyses were performed with the use of Stata 12 software or Golden Helix SNP & Variation Suite software (version 8.1.4).[26] A detailed description of the methods is provided in the Supplementary Appendix.

RESULTS

PARTICIPANT CHARACTERISTICS

The weighted mean age of the study participants was 59.9 years. The participants had weighted mean cholesterol values as follows: LDL cholesterol, 129.9 mg per deciliter (3.36 mmol per liter); high-density lipoprotein (HDL) cholesterol, 52.3 mg per deciliter (1.35 mmol per liter); and non-HDL cholesterol, 155.3 mg per deciliter (4.02 mmol per liter) (Table S3 in the Supplementary Appendix). Seven variants were included in the *PCSK9* genetic score and six variants in the *HMGCR* genetic score (Tables S4 through S7 in the Supplementary Appendix). There were no significant differences in any nonlipid baseline characteristics between the groups being compared, thus showing that assignment to each group was indeed random (Table 1).

CARDIOVASCULAR EVENTS

As expected, participants in the group with higher *PCSK9* genetic scores had a lower mean LDL

Table 1. Baseline Characteristics of the Participants, According to *PCSK9* Genetic Score.*

Characteristic	Below Median Score (N = 57,064)	Above Median Score (N = 55,708)	P Value
Lipids (mg/dl)			
LDL cholesterol	132.6±35.2	128.4±35.4	5.6×10^{-16}
HDL cholesterol	52.4±15.6	52.9±15.8	5.4×10^{-5}
Triglycerides			
Median	121.4	116.1	6.8×10^{-10}
Interquartile range	82–164	79–158	
Non-HDL cholesterol	157.6±37.5	153.1±38.2	1.8×10^{-16}
Nonlipid characteristics			
Age (yr)	61.3±7.2	61.4±7.2	0.24
Female sex (%)	58.2	58.1	0.68
Blood pressure (mm Hg)			
Systolic	127.7±17.5	127.8±17.2	0.43
Diastolic	74.9±9.9	75.0±10.3	0.36
Weight (kg)	76.9±16.7	76.9±16.2	0.75
Body-mass index†	27.5±5.3	27.7±5.0	0.17
Ever smoked (%)	54.1	54.3	0.28

* Plus–minus values are means ±SD. The weighted *PCSK9* genetic score was calculated for each participant by adding the number of low-density lipoprotein (LDL) cholesterol–lowering alleles that the person had inherited at each variant that was included in the score, weighted by the effect of each variant on LDL cholesterol levels measured in milligrams per deciliter. Values in the table represent weighted mean values of the baseline characteristics for the entire study sample (for age and sex) or from the prospective cohort studies (for all other variables) in either group, after combining study-specific estimates in an inverse-variance–weighted meta-analysis. To convert the values for LDL, high-density lipoprotein (HDL), and non-HDL cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

cholesterol level than those in the group with lower *PCSK9* scores (difference, −4.2 mg per deciliter [−0.11 mmol per liter]; $P=5.6\times10^{-16}$), as well as a lower mean level of non-HDL cholesterol (difference, −4.5 mg per deciliter [−0.12 mmol per liter]; $P=1.8\times10^{-16}$), a lower median level of triglycerides (difference, −5.3 mg per deciliter [−0.06 mmol per liter]; $P=6.8\times10^{-10}$), and a higher mean level of HDL cholesterol (difference, 0.5 mg per deciliter [0.01 mmol per liter]; $P=5.4\times10^{-5}$) (Table 1). Participants in the group with higher *PCSK9* genetic scores had an 8.4% lower risk of myocardial infarction or death from coronary heart disease (odds ratio, 0.92; 95% confidence interval [CI], 0.88 to 0.95), as well as similarly lower risks of major coronary events, major vascular events, myocardial infarction, and death from coronary heart disease (Fig. S2 in the Supplementary Appendix). In dose–response analyses, increasing *PCSK9* scores were associated with a stepwise decrease in LDL cholesterol levels and a corresponding stepwise decrease in the risk of myocardial infarction or death from coronary heart disease (Fig. 1A). Indeed, when the effects of each *PCSK9* score and the individual *PCSK9* variants included in these scores were plotted, there was a dose-dependent log-linear association between *PCSK9*-mediated lower LDL cholesterol levels and the risk of myocardial infarction or death from coronary heart disease (Fig. S3 in the Supplementary Appendix). The effect of the *PCSK9* score on the risk of myocardial infarction or death from coronary heart disease was similar in all subgroups studied (Fig. S4 in the Supplementary Appendix).

In similar analyses using the *HMGCR* genetic score, participants in the group with higher *HMGCR* scores had a mean LDL cholesterol level that was lower by 3.2 mg per deciliter (0.08 mmol per liter) than participants with lower

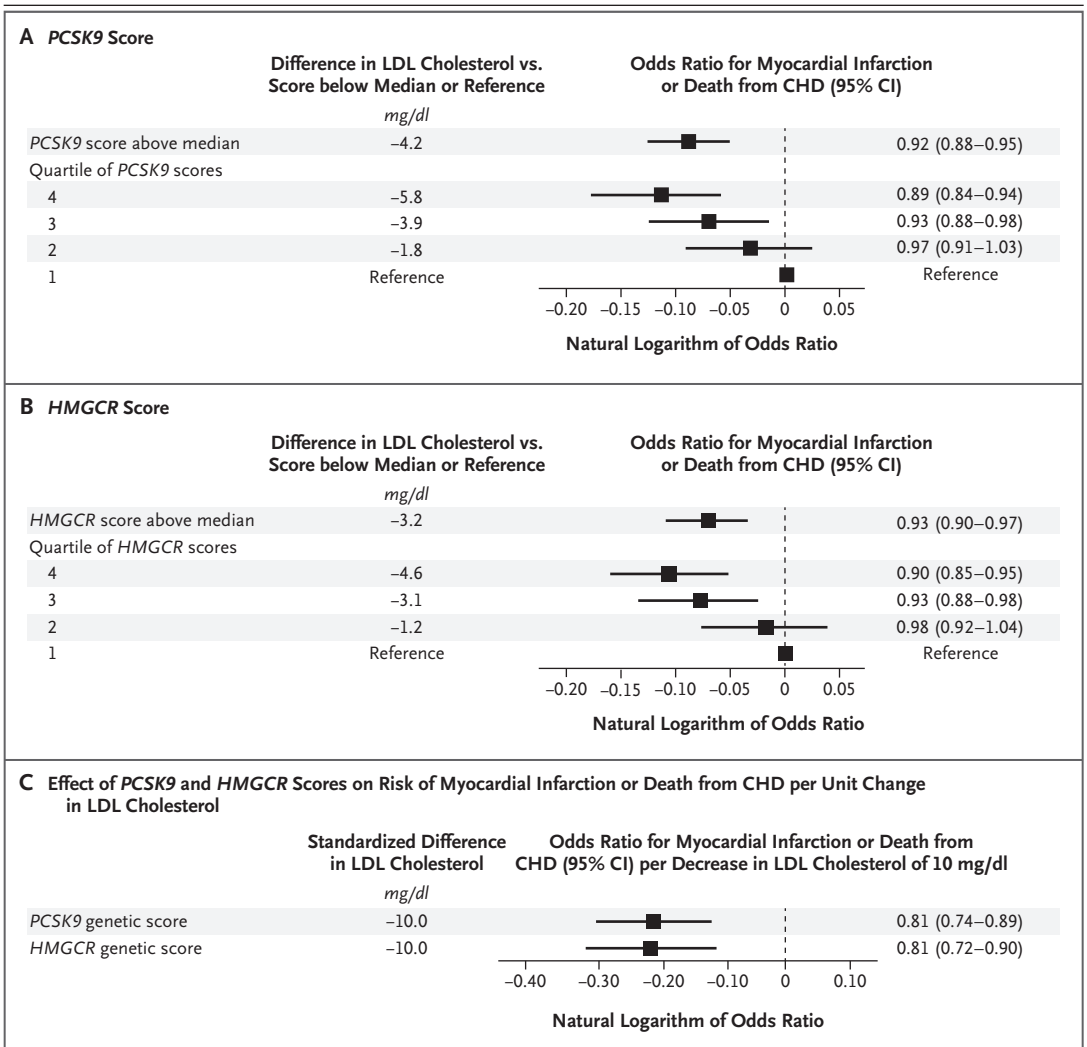

Figure 1. Effect of *PCSK9* and *HMGCR* Genetic Scores on the Risk of Myocardial Infarction or Death from Coronary Heart Disease.

For each study participant, we calculated a weighted *PCSK9* genetic score and a weighted *HMGCR* score by adding the number of low-density lipoprotein (LDL) cholesterol–lowering alleles that the person had inherited at each variant that was included in either score, weighted by the effect of each variant on LDL cholesterol levels measured in milligrams per deciliter. A total of 10,401 primary cardiovascular events (myocardial infarction or death from coronary heart disease [CHD]) were included in the analysis. Of these events, 5508 (1528 prevalent myocardial infarctions and 3980 incident myocardial infarctions or deaths from CHD) occurred in the prospective cohort studies and 4893 in the case–control studies. Across the included studies, the median weighted *PCSK9* score was 12.7 (range, 0 to 24.5), and the median weighted *HMGCR* score was 16.8 (range, 4.1 to 26.7). Boxes represent point estimates of effect. Lines represent 95% confidence intervals (CIs).

HMGCR scores ($P=2.9\times10^{-15}$) and a 6.6% lower risk of myocardial infarction or death from coronary heart disease (odds ratio, 0.93; 95% CI, 0.90 to 0.97) (Fig. 1B). As with the *PCSK9* score, the *HMGCR* score had a very consistent effect on each of the secondary outcomes and a similar effect in all subgroups studied.

After adjustment for a standard decrement of 10 mg per deciliter in the LDL cholesterol level, *PCSK9* variants were associated with an 18.9% decrease in the risk of myocardial infarction or death from coronary heart disease (odds ratio, 0.81; 95% CI, 0.74 to 0.89) and *HMGCR* variants were associated with a nearly identical 19.1%

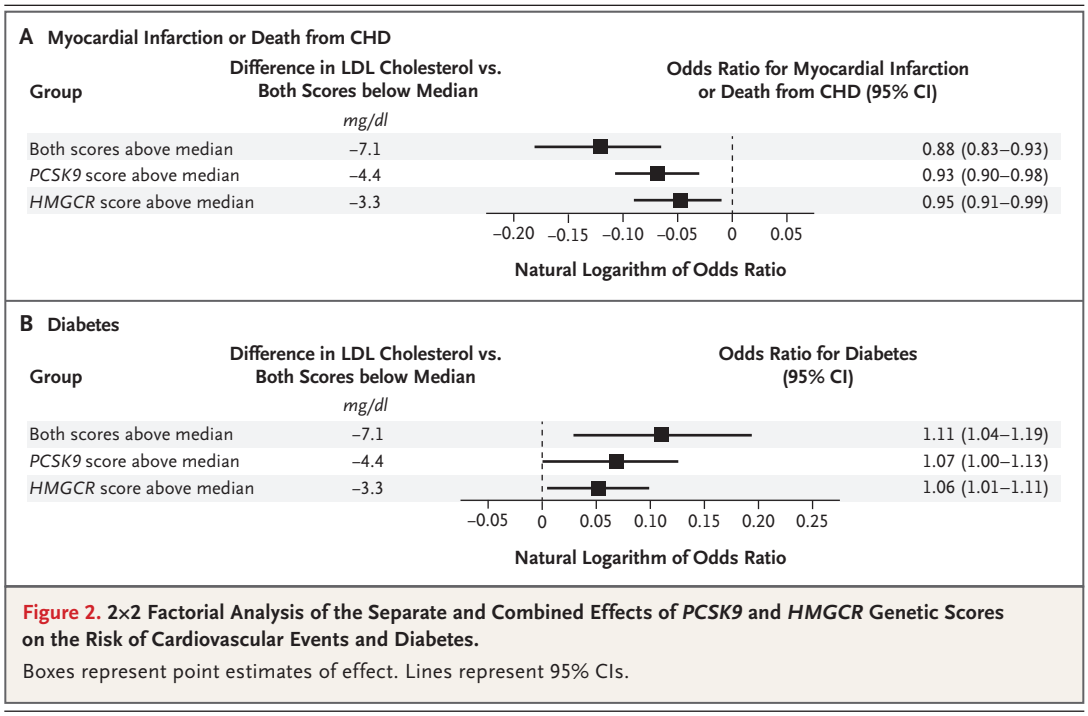

Figure 2. 2×2 Factorial Analysis of the Separate and Combined Effects of *PCSK9* and *HMGCR* Genetic Scores on the Risk of Cardiovascular Events and Diabetes.

Boxes represent point estimates of effect. Lines represent 95% CIs.

decrease in risk (odds ratio, 0.81; 95% CI, 0.72 to 0.90) (Fig. 1C). The effects of the *PCSK9* and *HMGCR* scores were very similar for all of the cardiovascular outcomes studied (Fig. S5 in the Supplementary Appendix). In the 2×2 factorial analysis, the *PCSK9* and *HMGCR* genetic scores had additive effects on LDL cholesterol and the corresponding risk of cardiovascular events (Fig. 2A).

In external validation analyses involving up to 62,240 case patients with coronary heart disease and 127,299 controls without such disease, the *PCSK9* genetic score (odds ratio, 0.84; 95% CI, 0.80 to 0.88) and *HMGCR* genetic score (odds ratio, 0.84; 95% CI, 0.81 to 0.89) had nearly identical associations with the risk of coronary heart disease per decrease of 10 mg per deciliter in the LDL cholesterol level (Figs. S6, S7, and S8 in the Supplementary Appendix). Mendelian randomization–Egger analyses showed that the effect of both *PCSK9* and *HMGCR* variants on the risk of cardiovascular disease was due entirely to their LDL cholesterol–lowering effect, with no evidence for any significant pleiotropic effects (Figs. S9 and S10 in the Supplementary Appendix).

RISK OF DIABETES

Participants in the group with higher *PCSK9* scores had a 6.1% higher risk of diabetes than those in the group with lower *PCSK9* scores (odds ratio, 1.06; 95% CI, 1.02 to 1.11). After adjustment for a standard decrement of 10 mg per deciliter in the LDL cholesterol level, *PCSK9* variants were associated with an 11.2% increase in the risk of diabetes (odds ratio, 1.11; 95% CI, 1.04 to 1.19). This effect was very similar to the 12.7% increase in the risk of diabetes per 10 mg per deciliter decrease in the LDL cholesterol level that was associated with *HMGCR* variants (odds ratio, 1.13; 95% CI, 1.06 to 1.20) (Fig. 3). Both the *PCSK9* and *HMGCR* genetic scores appeared to have dose-dependent effects on the risk of diabetes. When present together in the 2×2 factorial analysis, the *PCSK9* and *HMGCR* variants had additive effects on the risk of diabetes (Fig. 2B).

Among persons without prevalent diabetes at baseline, neither the *PCSK9* genetic score nor the *HMGCR* genetic score was significantly associated with baseline fasting plasma glucose levels (difference in plasma glucose level for each 10 mg per deciliter decrease in LDL cholesterol level for *PCSK9* score, 0.26 mg per deciliter [0.01 mmol per liter]; P=0.33; difference for *HMGCR* score, 0.42 mg per deciliter [0.02 mmol per liter]; P=0.10). Among persons with impaired fasting glucose levels at baseline (≥100 mg per deciliter [5.6 mmol per liter]), both the *PCSK9* and the *HMGCR* genetic scores were associated with a

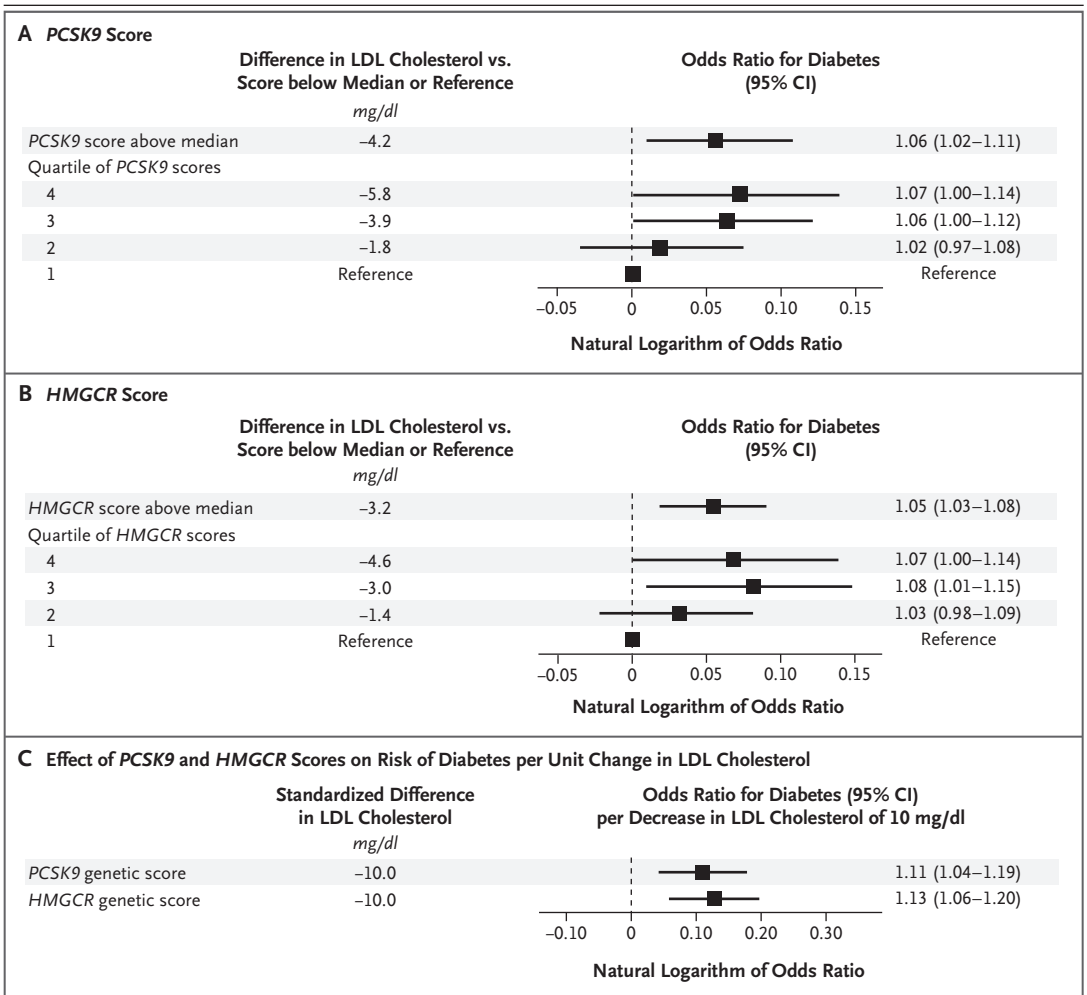

Figure 3. Dose–Response Relationship between *PCSK9* and *HMGCR* Scores and Risk of Diabetes.

A total of 10,635 cases of diabetes were included in the analysis. Of these cases, 4340 were prevalent at baseline and 6295 incident cases occurred during follow-up in the prospective cohort studies. The case–control studies provided data on cardiovascular disease but did not provide information on diabetes status and thus were not included in the analysis of diabetes risk. Boxes represent point estimates of effect. Lines represent 95% CIs.

higher risk of incident diabetes per decrease of 10 mg per deciliter in the LDL cholesterol level (odds ratio for *PCSK9* score, 1.22; 95% CI, 1.03 to 1.45; odds ratio for *HMGCR* score, 1.19; 95% CI, 1.00 to 1.41). By contrast, among persons with normal fasting glucose levels at baseline, neither the *PCSK9* nor the *HMGCR* genetic score was associated with an increased risk of incident diabetes (odds ratio for *PCSK9* score, 0.99; 95% CI, 0.84 to 1.17; odds ratio for *HMGCR* score, 1.04; 95% CI, 0.89 to 1.22) (Fig. 4).

REPLICATION AND ADDITIONAL ANALYSES

In additional analyses designed to evaluate the role of LDL receptor–mediated pathways as a potential common mechanism by which PCSK9 and HMGCR inhibition may increase the risk of diabetes, a genetic score consisting of variants in the gene encoding the LDL receptor (*LDLR*) had a very similar effect on the risk of diabetes per unit decrease in the LDL cholesterol level as compared with the *PCSK9* and *HMGCR* genetic scores (Fig. S11 in the Supplementary Appendix).

In a test of replication involving up to 86,196 participants of European descent (with 22,669 cases of diabetes) who were enrolled in the DIAGRAM consortium studies, the *PCSK9* and *HMGCR* genetic scores had very similar effects on the risk of diabetes per decrease of 10 mg per deciliter in the LDL cholesterol level (odds ratio

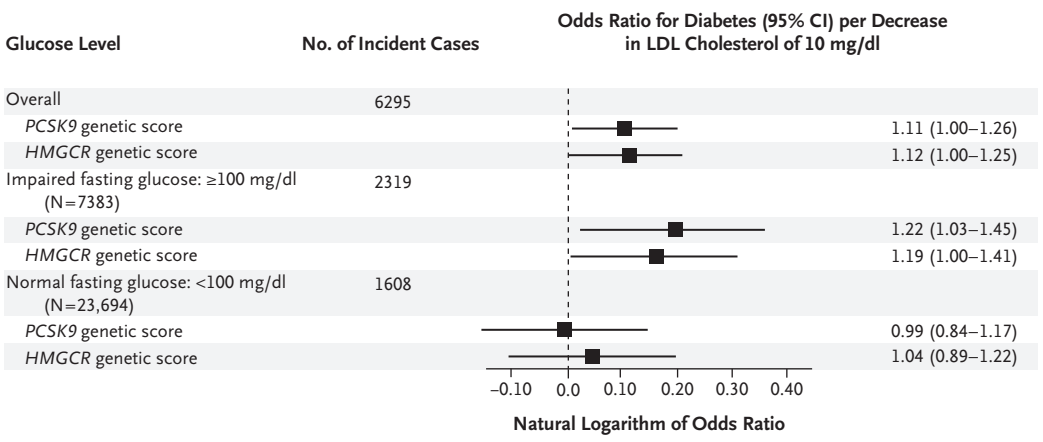

Figure 4. Effect of *PCSK9* and *HMGCR* Scores on the Risk of Incident Diabetes.

A total of 6295 incident cases of diabetes occurred during follow-up in the prospective cohort studies. After the exclusion of participants with prevalent diabetes, baseline fasting plasma glucose levels were available for 31,077 participants. The main analysis included all the participants after the exclusion of 4340 participants with prevalent diabetes; the subgroup analysis that was stratified according to fasting plasma glucose level included the 31,077 participants without prevalent diabetes for whom baseline fasting plasma glucose levels were available. Boxes represent point estimates of effect. Lines represent 95% CIs.

for *PCSK9* score, 1.08; 95% CI, 1.02 to 1.15; odds ratio for *HMGCR* score, 1.08; 95% CI, 1.02 to 1.14) (Figs. S12, S13, and S14 in the Supplementary Appendix). In additional analyses involving up to 133,100 persons enrolled in the Meta-Analyses of Glucose and Insulin-Related Traits Consortium studies,[27] the *PCSK9* and *HMGCR* genetic scores had very similar effects on plasma glucose levels 2 hours after an oral glucose challenge (effect of *PCSK9* score per 10 mg per deciliter decrease in LDL cholesterol, 1.55 mg per deciliter; 95% CI, 0.46 to 2.63 [0.09 mmol per liter; 95% CI, 0.03 to 0.15]; effect of *HMGCR* score per 10 mg per deciliter decrease in LDL cholesterol, 1.44 mg per deciliter; 95% CI, 0.11 to 2.77 [0.08 mmol per liter; 95% CI, 0.01 to 0.15]). These effects were quantitatively similar to the effect of the *PCSK9* 46L loss-of-function allele alone on both the risk of diabetes (odds ratio, 1.09; 95% CI, 0.98 to 1.23) and on plasma glucose levels 2 hours after an oral glucose challenge (effect per 46L allele, 1.51 mg per deciliter; 95% CI, 0.00 to 3.02 [0.08 mmol per liter; 95% CI, 0.00 to 0.17]).

Unlike the *HMGCR* genetic score, the *PCSK9* genetic score was not associated with weight, body-mass index, waist circumference, or waist-to-hip ratio in up to 339,224 participants enrolled in the Genetic Investigation of Anthropometric Traits consortium studies (Table S8 in the Supplementary Appendix).[28]

DISCUSSION

We found that genetic variants that mimic the effect of PCSK9 inhibitorshad remarkably similar effects on the risk of cardiovascular events and the risk of diabetes as compared with variants that mimic the effect of statins when measured per unit change in the LDL cholesterol level. Furthermore, we found that when variants that mimic the effect of PCSK9 inhibitors and statins were present together, they had independent and additive effects on the risk of both cardiovascular events and diabetes.

Our finding that *PCSK9* and *HMGCR* variants were associated with approximately the same effect on the risk of cardiovascular disease per unit decrease in the LDL cholesterol level suggests that treatment with a PCSK9 inhibitor should reduce the risk of cardiovascular events by approximately the same amount as treatment with a statin. Therefore, treatment with a PCSK9 inhibitor, used either alone or in combination with a statin, should reduce the risk of cardiovascular events by approximately 20% per decrease of 1.0 mmol per liter (39 mg per deciliter) in the LDL cholesterol level.[29]

Our finding that variants in *PCSK9* and *HMGCR* were associated with very similar effects on the risk of diabetes per unit decrease in the LDL cholesterol level implies that, like statins,

PCSK9 inhibitors may also increase the risk of new-onset diabetes. However, the increased risk of diabetes that was associated with both *PCSK9* and *HMGCR* variants appeared to be confined to persons with impaired fasting glucose levels. Therefore, as with statins, any potential increased risk of new-onset diabetes during treatment with a PCSK9 inhibitor is likely to be confined to persons with impaired fasting glucose levels.

Although variants that mimic the effect of PCSK9 inhibitors and statins were associated with an increased risk of diabetes, the corresponding proportional reduction in cardiovascular risk was much greater than the increased risk of diabetes. Therefore, as with statins, the reduction in cardiovascular risk with PCSK9 inhibitors should far exceed any potential increased risk of diabetes. Furthermore, we found that both *PCSK9* and *HMGCR* variants were associated with a decreased risk of cardiovascular events among persons with diabetes and those without diabetes. This finding is consistent with the results of meta-analyses showing that statins are associated with the same proportional reduction in the risk of cardiovascular events in persons with diabetes as in those without diabetes.[30] Therefore, like statins, PCSK9 inhibitors should reduce the risk of cardiovascular events equally well among persons with diabetes and those without diabetes.

The mechanism by which *PCSK9* and *HMGCR* variants increase the risk of diabetes is unclear. However, it is unlikely to be mediated by weight gain because unlike *HMGCR* variants, *PCSK9* variants are not associated with obesity or its subphenotypes, such as weight, body-mass index, or waist circumference. Instead, the mechanism may involve an LDL receptor–mediated pathway. We found that each set of gene-specific variants in *PCSK9*, *HMGCR*, and *LDLR* had a very similar effect as the other sets on the risk of diabetes per unit decrease in the LDL cholesterol level. This finding is consistent with the fact that both PCSK9 and HMGCR inhibitors ultimately reduce plasma LDL cholesterol levels by increasing the density of LDL receptors.[31] It is also consistent with the observation that persons with familial hypercholesterolemia appear to have a lower prevalence of diabetes than unaffected relatives.[32]

The genetic evidence suggests that PCSK9 and HMGCR inhibition, possibly acting through an LDL receptor–mediated pathway, may cause mildly impaired glucose tolerance (as suggested by higher plasma glucose levels 2 hours after an oral glucose challenge) without materially increasing fasting glucose levels, which may then lead to an increased likelihood of incident diabetes among persons who have impaired fasting glucose levels. This conclusion is consistent with data from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), in which treatment with rosuvastatin was associated with an increased risk of diabetes but not an increase in fasting plasma glucose levels, and virtually all of the increased risk of diabetes occurred among persons with impaired fasting glucose levels.[33]

Our study has limitations. Lifelong exposure to decreased levels of LDL cholesterol that are mediated by genetic variants is associated with much greater reductions in the risk of cardiovascular disease per unit decrease in the LDL cholesterol level than is short-term pharmacologic treatment.[34] Therefore, the effect of *PCSK9* variants on the risk of cardiovascular events (and probably diabetes) that was estimated is likely to be quantitatively much larger than the effect of treatment with a PCSK9 inhibitor observed in the ongoing outcome trials as measured according to the unit decrease in the LDL cholesterol level. However, having first established that variants that mimic the effect of PCSK9 inhibitors and statins have biologically equivalent effects on the risk of cardiovascular events and diabetes per unit decrease in the LDL cholesterol level, we believe it is reasonable to anticipate that PCSK9 inhibitors and statins are likely to have therapeutically equivalent effects on the risk of cardiovascular events and diabetes per unit decrease in the LDL cholesterol level.[35,36] In addition, it is important to note that monoclonal antibodies bind extracellular PCSK9 and therefore may not have the same biologic effect as *PCSK9* variants that lower LDL cholesterol levels.

In conclusion, we found that variants in *PCSK9* and *HMGCR* were associated with approximately the same effects on the risk of cardiovascular events and very similar effects on the risk of diabetes per unit decrease in the LDL cholesterol level. We also found that these effects were independent and additive.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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